

Are Newer Antiepileptic Drugs Associated with Improved Safety In Pregnancy Compared to Older Antiepileptic Drugs?

Comparative Safety of Antiepileptic Drugs During Pregnancy.

Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, Holmes LB; North American AED Pregnancy Registry. North American AED Pregnancy Registry. *Neurology* 2012;78:1692–1699.

OBJECTIVE: To assess the safety of the newer antiepileptic drugs (AEDs) during pregnancy. **METHODS:** The study population was pregnant women who enrolled in the North American AED Pregnancy Registry between 1997 and 2011. Data on AED use and maternal characteristics were collected through phone interviews at enrollment, at 7 months' gestation, and postpartum. Malformations were confirmed by medical records. The risk of major malformations was calculated among infants exposed to specific AEDs in monotherapy during the first trimester of pregnancy and among an unexposed group. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated with logistic regression. **RESULTS:** The risk of major malformations was 9.3% (30 of 323) for valproate, 5.5% (11 of 199) for phenobarbital, 4.2% (15 of 359) for topiramate, 3.0% (31 of 1,033) for carbamazepine, 2.9% (12 of 416) for phenytoin, 2.4% (11 of 450) for levetiracetam, and 2.0% (31 of 1,562) for lamotrigine. Compared with lamotrigine, the RR was 5.1 (95% CI 3.0–8.5) for valproate, 2.9 (1.4–5.8) for phenobarbital, and 2.2 (1.2–4.0) for topiramate. The proportion of women with epilepsy who had seizures during pregnancy ranged from 23% for valproate to 31% for lamotrigine. Valproate was associated with a higher risk of neural tube defects, hypospadias, cardiac defects, and oral clefts and phenobarbital with a higher risk of cardiac defects and oral clefts; 5 infants exposed to topiramate (1.4%) had a cleft lip. **CONCLUSIONS:** AEDs such as valproate and phenobarbital were associated with a higher risk of major malformations than newer AEDs such as lamotrigine and levetiracetam. Topiramate was associated with an increased risk of cleft lip compared with that of a reference population.

Commentary

As a group, antiepileptic drugs (AEDs) are associated with an increased risk of major congenital malformations (MCMs) (1). Older AEDs are the best studied. Valproate (VPA) is consistently associated with an increased risk of MCMs including an increased risk of spina bifida (2). Phenobarbital (PB) exposure increases the risk of MCMs, including oral clefts (3). Although not consistent among published studies, some have found an increased risk of neural tube defects in association with carbamazepine (CBZ) therapy (4, 5). Less is known about the risk of MCMs in association with newer AEDs (6).

Better understanding of these agents' impact on the developing fetus is critical, as AEDs such as lamotrigine (LTG), levetiracetam (LEV), and topiramate (TPM) are being used in increasing numbers. Internationally, the epilepsy community has established different registries to address this issue. The North American Registry was established in 1997 (7). Women using AEDs for any indication are enrolled early in pregnancy. Gathering information on AEDs used for any indication is important, as many AEDs are used for multiple indications including

headaches, pain, and mood disorders. Hopefully, with increasing enrollment, there will be enough numbers to do analyses that compare outcomes among the different indications.

Hernández-Díaz and colleagues (7) presented updated analyses from the North American Pregnancy Registry. The outcomes of interest were MCMs diagnosed before 12 completed weeks after birth. It is important to note that different registries have variable periods of follow-up. For example, the EURAP register collects information through 12 months of age (8). Excluded were 1) minor anomalies, birthmarks, deformities, and anatomic findings by ultrasound not identified by examining pediatrician, 2) complications of prematurity, 3) genetic disorders, and 4) chromosomal abnormalities. The investigators identified multiple reference groups: 1) the primary reference group was women exposed to LTG; 2) an internal reference group of pregnant women without epilepsy, not taking an AED who have been recruited among friends and family of AED exposed subjects; and 3) an external reference group of 206,224 infants born at Brigham and Women's Hospital in Boston, MA. Using the LTG group as an internal comparison provides advantages, including offering a direct comparison among AEDs and minimizing confounding.

The investigators used a multivariate logistic regression analysis. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated. Multiple confounders were controlled for,



including maternal age, race, education, alcohol use, cigarette smoking, periconceptual folic acid use, illicit drug use, chronic diseases, and calendar year. Interestingly, none of these confounders affected the RR of MCMs in the exposed groups; therefore, crude RRs were provided.

In the final analysis, 4,889 out of 5,667 women taking an AED as monotherapy during the first trimester were eligible, and there were 442 eligible women out of 479 in the internal comparison group. AEDs with enrolled subjects (in order of descending enrollment) were LTG ($n = 1,562$), CBZ ($n = 1,033$), LEV ($n = 450$), phenytoin (PHT) ($n = 416$), TPM ($n = 359$), VPA ($n = 323$), PB ($n = 199$), oxcarbazepine (OXC) ($n = 182$), gabapentin (GBP) ($n = 145$), zonisamide (ZNS) ($n = 90$), and clonazepam (CZP) ($n = 64$). The numbers for LEV and TPM were the highest among published reports. It is difficult to draw any formal conclusions from this analysis about OXC, GBP, ZNS, and CZP, as the sample sizes were all small. Further enrollment and data from other studies are needed to better understand the effects of these AEDs on MCM outcomes.

Consistent with other studies (1, 2, 4, 8), VPA was associated with the highest MCM risk (9.3 (95% CI: 6.4–13.0)). PB was associated with a risk of 5.5% (95% CI: 2.8–9.7). LTG was associated with the lowest risk (2.0 (95% CI: 1.4–2.8)). The risk of MCMs in LEV exposed pregnancies was 2.4% (95% CI: 1.2–4.3). The risk among TPM users was 4.2% (95% CI: 2.4–6.8). Compared with LTG, the RR of VPA was 9.0 (95% CI: 3.4–23.3), PB was 5.1 (95% CI: 1.8–14.9), LEV was 1.2 (95% CI: 0.6–2.5), and TPM was 2.2 (95% CI: 1.2–4.0).

As demonstrated in other studies, there was a dose effect of VPA (8). Among those pregnancies with MCMs, the median daily dose was 1000 mg, whereas the median daily dose for those without was 750 mg. Regarding the other AEDs, there was no difference in median average daily dose among exposed infants with or without MCMs. This lack of a dose effect is in contrast with the EURAP register, which revealed a dose effect for CBZ, LTG, and PB (8). In this current analysis, the investigators did not provide either the sample sizes of different dose groups as presented in EURAP study. Therefore, it is difficult to directly compare these results.

When looking at specific malformations, VPA was associated with an increased risk of neural tube defects, hypospadias, and cardiovascular malformations. Cardiovascular malformations were more commonly found among PB-exposed pregnancies. The risk of oral clefts in association with different AEDs used as monotherapy is an evolving story. The North American Registry originally published a risk of 7.3 per 1,000 among LTG monotherapy users (9). With an increased sample size the reported risk is now 4.5 per 1,000 (95% CI: 2.0–8.8). Other studies have reported even lower risks (4, 6). Similar to other studies (6, 10) the reported risk for oral clefts in association with TPM (14 per 1,000 (95% CI: 5.1–31.0)) is higher than the expected risk in the general population. This reported increased risk of oral clefts led to the current FDA Category D status.

The investigators did an exploratory analysis of the effect of seizures on the risk of MCMs. Studies found the risk to be associated with AED use (1). However, it is very difficult to

compare groups of women with epilepsy who are treated versus those who are not, as they likely have different disease severity. The results of this analysis found that AED groups with higher frequency of seizures during pregnancy had lower risk of malformations. Within those AED groups associated with higher MCM risk (VPA and PB), women who had no seizures during the pregnancy had a higher risk of MCMs compared with women who had seizures. These analyses were based on small number, and the results highlight that the impact of seizures—including seizure frequency and different seizure types on pregnancy outcomes—needs further study.

In this analysis of the outcome of MCMs among women exposed to different AEDs, monotherapy, VPA, and PB were associated with this highest MCMs. LTG and LEV were associated with the lowest risk. As in other studies, TPM was associated with an increased risk of oral clefts. Further study is needed to understand the effects of OXC, ZNS, CZP, and GBP as well as the impact of seizures on developing fetuses.

by Alison M. Pack, MD, MPH

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